THALIDOMIDE: 40 YEARS ON

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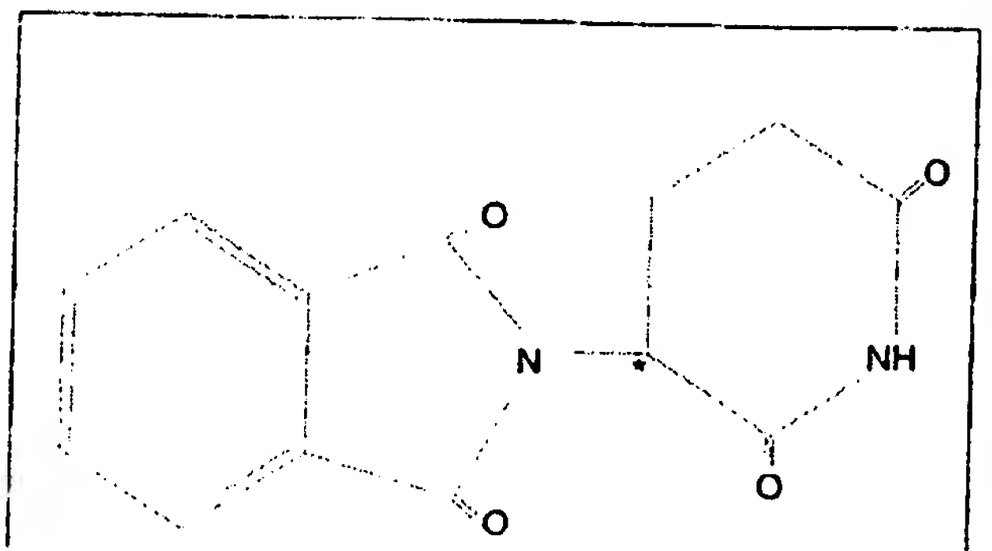
SUMMARY Thalidomide was marketed in the late-1950s as a sedative and tranquilliser of exceptionally low general toxicity, but in 1961 it was implicated separately by Lenz and MacBride as the cause of the epidemic of congenital malformations that had been puzzling the world for some years. It is a very potent teratogen in humans, but in few other mammalian species; damage to the embryo is produced at specific stages of gestation, but the mechanism of embryopathic action is still not understood. Following the withdrawal of the drug worldwide, it was consigned to the history of medical tragedies. In 1965, however, Sheskin discovered that it was effective in treating erythema nodosum leprosum, a distressing complication of leprosy. As the drug is neither an antibiotic nor an analgesic, its action was assumed to be immunosuppressive. In Brazil the drug was used widely with few regulatory controls, since when more than 100 cases of congenital malformation have appeared. Sheskin's discovery led to the experimental use of thalidomide in many other indications thought to possess some immunological component. In some cases, e.g. Behçet's syndrome, graft-versus-host disease and aphthous ulceration in HIV-positive patients, the drug has been shown to possess some efficacy. And there is some evidence that it inhibits the replication of one of the immunodeficiency viruses. The AIDS community in the US has exerted much pressure on the FDA to allow the drug on to the market, although the use of a potent immunosuppressive drug of unknown mechanism in an immunodeficiency condition raises further questions. Thalidomide is not always beneficial; its use is associated with an increased mortality in epidermal necrolysis. In 1991, D'Amato confirmed it possessed antiangiogenic properties and this led to further trials in malignant conditions. Results were mixed, but those in multiple myeloma gave some grounds for optimism. In 1998, the FDA announced its extraordinary decision to grant marketing approval for thalidomide. (*Int J Clin Pract* 2001; **55(9)**: 627-631)

On 25 December 1956, a girl with no ears was born in Stolberg, Germany. A man who worked at the local pharmaceutical company, Chemie Grünenthal, had been given free supplies of a newly developed sedative/tranquilliser for his pregnant wife. This incident heralded the spread to many other countries of a major epidemic of congenital deformities. Most noticeably and frequently the limbs were affected, with amelia (Gr. lack of limb) or phocomelia (Gr. seal limb). In addition to these limb reduction deformities, there were malformations affecting the heart, ears, eyes and alimentary tract. Up to 12,000 babies were affected and a large minority died soon after birth, most because of serious cardiac anomalies. There was an unknown number of spontaneous abortions.

Although it was obvious that some embryopathic agent was responsible for the epidemic, its nature was a matter for speculation, with suspicion falling on radiation, a virus and many chemical products and contaminants. Thalidomide (α-phthalimido-glutarimide), developed by Grünenthal, was first identified as the teratogen by Lenz, in a paper read to a paediatric meeting in Dusseldorf on 18 November 1961. The molecule possesses optical isomerism, has a chiral centre as shown in Figure 1, and consists of S(-) and R(+) enantiomers which interconvert rapidly under physiological conditions.



* chiral centre

Figure 1. Structure of thalidomide

The enantiomers and the racemate have different chemical, toxicological and therapeutic properties, although there are contradictory results. Thalidomide is susceptible to spontaneous (non-enzymatic) hydrolytic cleavage, and the derivatives, again, have different properties. The identity of the teratogen[1,2] was confirmed from maternal histories of medication, the correlation month by month between

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incidence (in time and place) and sales figures and, later, by teratogenicity studies in animals. For each type of malformation, exposure during a defined period of embryogeny is required, ranging from 34 to 50 days after the last menstrual period. In many cases, therefore, the woman would be unaware she was pregnant.

Thalidomide was welcomed by prescribers because it appeared to have much less acute toxicity than the available alternatives – essentially barbiturates. It was later found to have immunosuppressive properties. Only a small battery of toxicity tests was conducted, however. The mode of action of the drug was not elucidated and the mechanisms of the sedative, teratogenic and immunosuppressive actions are still not understood. The efficient sales department at Grünenthal ensured that it was marketed both as a single-drug product and as combination products for treating any condition thought to involve anxiety. The drug was specifically advertised for morning sickness. Total sales figures were enormous (14,580 kg in 1960), with deformities peaking nine months later at 1515 in Germany in 1961. In the UK alone, combination products included Asmaval, Tensival, Valgis and Valgraine.

As a teratogen the drug is highly species-specific, very potent and acts at highly specific stages of embryogenesis. The general toxicity is very low in laboratory animals and teratogenicity is seen only in the rabbit and some primates. The sedative action seen in man is less marked in laboratory animals. A less serious adverse effect is peripheral neuropathy and the drug is immunologically active.

In America, the Food and Drug Administration (FDA), using powers conferred by the existing Food, Drugs and Cosmetics Act 1938, had prevented the marketing of the new sedative because insufficient data were available. It is to the great credit of FDA's medical assessor that the incidence of deformities induced by the drug, which would have had the propriety name Kevadon, was relatively small in the US. Women of child-bearing potential were excluded from the clinical trials that had been permitted in the US. The only cases of deformity that did occur involved cases where investigating doctors had not supervised this criterion adequately. In 1998, however, the drug was approved in the US, for a specific indication, subject to rigorous conditions. The use of thalidomide continued in Brazil, where many cases of phocomelia have appeared since 1965, because of regulatory negligence.

LEGAL ASPECTS

Thalidomide was immediately withdrawn from the market worldwide. Governments introduced new legislation to ensure that no tragedy of this kind could occur again. In the UK there was intense parliamentary debate, mirroring that in other countries, with pressure from patient groups for an exacting medicines control law and from the pharmaceutical industry for a more lenient statute. In the meantime, a voluntary scheme for medicines operated in the UK from 1963: pharmaceutical companies were invited to seek the advice of the Committee on Safety of Drugs (the so-called 'Dunlop Committee') before launching new products. The voluntary scheme was superseded when a statutory system of pre-marketing authorisation was at last introduced in September 1971, when licensing under the Medicines Act 1968 was first implemented; this system is still in operation today. Under the new act, product licences were issued by the licensing authority (the health ministers), advised by the Committee on Safety of Medicines, after assessment of safety, efficacy and quality. Regulations made under the act (and similar legislation in most other countries) ensured the introduction of reproductive toxicity tests for effects on the reproductive and neuroendocrine systems, and the embryo, fetus, neonate and pre-pubertal mammal were studied. A minimum of three tests is commonly required. If all these produce only negative results, then the drug is thought to be unlikely to harm mammalian reproduction. The three basic tests are embryotoxicity (which uses two species, high doses and short duration, covering the process of embryogenesis); perinatal pathology (using one species, covering prenatal and post-natal phases); fertility and general reproductive performance (which is lengthy, conducted in one species, uses relatively low doses starting two ovulatory cycles before mating and ending when some offspring are weaned). If there is doubt, multigeneration testing is undertaken and animals from any generation can be mated with untreated animals to determine the sex specificity of any effect noted. In the US, the existing Food, Drugs and Cosmetics Act of 1938 was amended, and stringent requirements for establishing the safety and efficacy of medicines before they could be marketed were introduced.

Legal battles about compensation took place between patients' associations and manufacturers in all countries where the devastating effects of the drug had been seen. In Germany, the main proceedings were held at Aachen in the vicinity of the Grünenthal headquarters. Various medical arguments were deployed by the company's lawyers, one of the most memorable being the claim that thalidomide (Contergan in Germany) was not itself teratogenic but was so beneficial to the conceptus that spontaneous deformities, which would normally have been eliminated by abortion, were preserved and malformed neonates were born. The turning point in the German proceedings occurred when court bailiffs searching the company's headquarters discovered a locked bunker containing much correspondence and documentation about the drug. When this material was revealed in court, it became clear that many of the claims for efficacy were not founded on proper clinical trials in the many indications concerned. Reports of adverse reactions had been suppressed, as had early suggestions that thalidomide might be the cause of the mysterious epidemic of malformations.[3]

In the UK, thalidomide was marketed under licence from the German developer by the Distillers Company under the derived name Distaval. By 1970 legal wrangling had reached a stalemate, and *The Sunday Times* attempted to

publish factual material on the state of play but was held to be in contempt as court proceedings had not been concluded. This ruling was upheld by higher courts, including the House of Lords (Attorney-General *v* Times Newspapers 1974). However, the newspaper took the matter to the European Court of Human Rights at Strasbourg, which has been the guardian of the European Convention on Human Rights since its creation in 1953. The right of *The Sunday Times* to publish an unprejudicial article was upheld (Article 10 of the Convention – Freedom of Expression) and British law about contempt had to be changed. This resulted in the enactment of the Contempt of Court Act 1981. Following the 1997 election in the UK, the new government adopted the Convention into UK domestic law.

THALIDOMIDE IN BRAZIL

Although thalidomide was withdrawn from clinical use in nearly all countries, this did not apply to Brazil, where it was used on a very wide scale for the treatment of leprosy from 1966. When an individual acquires the tuberculoid form of the disease, there is an immune response mediated by T cells, tuberculosis-like granulomas and few bacteria in the tissues. If the T cell response is compromised, however, lepromatous leprosy, with involvement of B lymphocytes and macrophages and many bacteria in the tissues, develops. This form of leprosy may be complicated by erythema nodosum leprosum (ENL), which is characterised by red, moist, painful nodules; fever is always present and there may be inflammation of joints, nerves and various organs. ENL may occur in single, mild episodes or may be severe and continuous with prostration and, occasionally, death.

In 1965 Jacob Sheskin[1] reported the serendipitous finding that thalidomide was extremely effective in the treatment of ENL, a conclusion confirmed by double-blind trials[2] in which only 10% of patients failed to benefit, and it was reintroduced widely in Brazil, where it is still manufactured at several sites. Unfortunately, medical supervision has been inadequate. According to the ABPST (Associaço Brasileira dos Portadores da Sindrome da Talidomida) patients' association, some 800 individuals claim to be victims. Of these, 122 are officially recognised cases of the 'second generation', the last born in 1995. There are 246 officially recognised cases of the first generation (pre-1963).

According to World Health Organisation guidelines,[3] the preferred treatment for lepromatous leprosy is multidrug therapy, consisting of rifampicin, clofazimine and dapsone. ENL requires specific treatment and responds to prednisolone 40 mg daily but a prolonged period of treatment may be needed, leading to serious corticosteroid adverse effects. Clofazimine has analgesic as well as antileprotic properties and ENL may respond to high doses. Thalidomide, with initial doses in excess of 100 mg per day, is regarded by many experts[4] as the treatment of choice for ENL, although its mode of action is unknown. It has no antileprotic or analgesic properties, and its efficacy is thought to result from immunological action.

It is essential that the use of the drug be strictly controlled, so that it cannot become available to any woman of child-bearing potential. It is to the everlasting shame of the government of Brazil that effective controls were not instituted. For many years thalidomide was sold over the counter in pharmacies without need of a doctor's prescription. The product carried no safety labelling in Portuguese (the mother tongue) or in diagrammatic form (there is a high rate of illiteracy). There was no follow-up or supervision of women receiving the drug. The drug is also marketed in Brazil for other indications, including AIDS and discoid lupus erythematosus.

RECENT USES OF THALIDOMIDE

Following the discovery of the drug's effectiveness in ENL, it has been used for many indications in trials and individual cases, especially in conditions with some immune component. The results, however, have not always been favourable. In toxic epidermal necrolysis, a significantly increased mortality,[5] possibly due to a paradoxical increase in TNF-α production, is associated with the use of the drug. Conditions in which successful use has been claimed include Behçet's syndrome,[6,10] aphthosis in HIV positive patients,[11] graft versus host disease[16,17] and cancer.[18,22] Thalidomide is used on an experimental (named patient) basis in the UK, where it is manufactured by Penn Pharmaceuticals.

Behçet's syndrome, with its distressing oral and genital ulcers, lacked an effective treatment until thalidomide was tried. Doses of 100-300 mg/day were found by several authors to produce substantial improvements.[6,10] Withdrawal of the drug was followed by a return of symptoms in many cases.[6] Seventy-three cases of severe recurrent aphthous stomatitis (including cases of Behçet's syndrome) received thalidomide or placebo in a crossover study. Some 50% on the drug, but only 9% on placebo, experienced complete remission.[11] Most relapsed three weeks after withdrawal of the drug.

The aphthous ulceration of the mouth and oesophagus and the resulting dysphagia which occur in HIV positive patients responds to the drug.[12,13] And thalidomide has been found to inhibit the replication of immunodeficiency virus type 1.[14] The protein known as tumour necrosis factor-alpha (TNF-α), and its messenger RNA, were also reduced, suggesting a possible role of the drug in inhibiting viral replication and reducing the TNF-α-induced systemic toxicity of HIV-1. Several small series[12] have shown that the drug is effective in aphthous ulceration in at least 19 patients. Using daily doses of 50-200 mg during the acute phase, complete remission occurred within 3-14 days. Maintenance therapy was effective. If reduction of TNF-α is found to occur in the other diseases responsive to thalidomide, this could provide a clue to further applications. A search is in progress for anti-TNF-α agents that are not toxic. However, work in leukaemia cell lines has shown that the release of TNF-α (by a known releasing agent) is enhanced, rather than diminished, by the drug.[15]

Graft versus host disease (GVHD) is quite different from the mucocutaneous conditions considered above, yet it responds to the immunosuppressive effects of thalidomide. The disease may develop in immunocompromised patients who receive transplants containing immunocompetent donor cells. Thalidomide improves the clinical condition of about 50% of patients with chronic GVHD following bone marrow transplantion in whom other therapies have failed. It is less effective in acute GVHD. In one of the largest trials reported to date,[16] 44 patients with chronic GVHD took 200 mg of the drug four times daily; this dose was titrated upwards to give a plasma concentration of 5 mg/l. A complete response was seen in 14 patients and a partial response in 12. In a larger series,[17] 80 refractory or high-risk patients received 100 mg of the drug four times daily, escalating to 200-300 mg four times daily. The overall response rate was 20%, with nine complete responses and seven partial responses.

Cancer was thought to be a target for thalidomide at an early stage. In 1965 two trials of the drug in wide ranges of advanced malignancies were published.[18,19] The results were very disappointing, however. Twenty-five years later there was renewed interest in the hypothesis that the teratogenic action of the drug might be due to interference with the development of blood vessels of the limb buds and affected organs. At this time D'Amato was examining the literature in search of antiangiogenic drugs that might be useful in cancer therapy, by depriving tumours of their blood supply. Thalidomide was considered to be a prime candidate for this work. D'Amato and colleagues demonstrated the ability of the drug to inhibit angiogenesis (induced by fibroblast growth factor) in a rabbit cornea assay.[20] It was then shown that angiogenesis inhibition by thalidomide analogues correlated with the teratogenic but not the sedative and immunosuppressive properties of the drug. This evidence was considered to justify the trial of this antiangiogenic drug in cancer again.

In the 1990s many trials were conducted in various types of cancer, generally with mixed but not very promising results. Trials in multiple myeloma produced the most hopeful results. In one study,[21] 89 patients with high-risk, refractory multiple myeloma received 200 mg/day titrated upwards, according to tolerance, to a maximum of 800 mg/day. In 11% of cases a response (measured by M protein analysis) of better than 75% was seen. In 9%, the response was 51-75%, and, in 14%, the response was 21-50%. In 30 responders, median cytoreduction was 61%. Following this work in 1998, another group[22] studied the effects of thalidomide combined wth chemotherapy in plasma cell leukaemia and fulminant multiple myeloma, with promising preliminary results.

In 1998 the FDA surprisingly granted approval to the Celgene Corporation for thalidomide (Thalomid) to be marketed for use in severe ENL. The most stringent and exacting requirements were imposed. Nevertheless, the decision was surprising, in view of the many unanswered, important questions about the drug.

MODE OF ACTION

Thalidomide acts as a sedative, a teratogen and an immunomodulatory drug, but its mechanism(s) of action are not understood in any of these roles. Quite apart from teratogenicity, it must be asked whether a drug with potent but unknown actions on the immune system should be used in AIDS and other serious illnesses. Various assertions have been made by enthusiasts, in some cases irresponsibly, with claims that the mode of action is known, but this is not the case. Biochemical and clinical findings have provided clues about mechanisms but the research effort is unorganised and more focused work is required. Teratology is now a well-advanced science and, after 40 years of progress, originally triggered by thalidomide itself, may be able to provide answers.

Certain criteria must be observed when these teratological studies are planned:

- Work should be conducted *in vivo*, in a susceptible species (preferably a primate; otherwise rabbits)
- Testing should occur at the sensitive period
- Testing should focus on susceptible primordia (e.g. limb buds or heart)
- Dosing should be high enough to produce positive results in all offspring, but without producing serious maternal toxicity
- The endpoint should occur shortly after the lesion has been produced
- Biochemical monitoring should enable metabolites, degradation products, isomers, etc, to be measured. The endpoint should be chosen to distinguish clearly between teratogens and non-teratogens
- The changes induced should be pronounced and explain abnormal development.

Since the appearance of thalidomide, relatively few investigators have observed these criteria. Nevertheless some clues to a possible mechanism have been found. One of the most interesting areas of investigation concerns the mesonephros. The mesonephros is able to stimulate chondrogenesis in chick and human limb buds *in vitro*. Thalidomide counteracts this ability. The mesonephros produces insulin-like growth factor (IGF-1) near the limb primordia, and this substance has been found able to replace the ability of the mesonephros to stimulate chondrogenesis, and to be angiogenic. Thalidomide has been found to abolish the stimulating effects of of IGF-1 on chondrogenesis and limb bud development. Furthermore, thalidomide inhibits the production of certain integrins, while IGF-1 can promote integrin production. Integrins are necessary for blood vessel formation, while thalidomide is antiangiogenic. Putting these findings together, it is possible to conjecture that thalidomide interferes with the role of IGF-1 during pre-limb and early limb bud stages. The fall in IGF-1 production causes a decrease in the production of certain integrins which affect cell migration vital to angiogenesis. Blood vessels do not form normally, and the early limb fails to develop.

CONCLUSION

Some enthusiasts believe there should be a renaissance of thalidomide and that it should be returned to the pharmaceutical marketplace. Others, mindful of the devastating teratogenicity seen in the epidemic and, later, in Brazil, consider this would be a mistake. The myth that beneath the horrors and nightmares of the past lies 'a wonder drug with a golden future bursting to get out'[23] should be debunked, in our present state of ignorance. Thalidomide, its enantiomers, metabolites, degradation products and analogues do not share identical toxicological and therapeutic profiles. The debate is confused and would be clarified by a clear-headed analysis of the risks and benefits of these different molecules in different indications. The risk of malformation seen in Brazil is known, because the regulatory authorities there are aware of the numbers of cases, and of the tonnage of drug manufactured year by year. The risk may be small in arithmetical terms, but the perceived risk[24] is very large, for the usual reasons.

Risk can undoubtedly be minimised by measures such as those stipulated by the FDA, where they can be enforced, but too little is known of the differential toxicity and clinical efficacy, and modes of action of these molecules. In the present state of knowledge, none of these compounds should be marketed, but should in general be available on a named-patient basis for research purposes. When there is a clear picture of the safety and efficacy of a particular compound in a particular indication, then regulators can take a well-informed decision.

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